doi 10.34172/aim.2020.34

Original Article

# Is Histopathological Evaluation of Hernia Sacs Necessary?

Check for updates

ARCHIVES OF

http://www.aimjournal.ir **MEDICINE** 

IRANIAN

Ugur Topal, MD<sup>1,2\*</sup>; Mustafa Gok, MD<sup>1</sup>; Muhammet Akyuz, MD<sup>1</sup>; Abdullah Bahadir Oz, MD<sup>1</sup>; Turkmen Bahadir Arikan, MD<sup>1</sup>; İsmail Solak, MD<sup>1</sup>; Kemal Deniz, MD<sup>3</sup>; Erdogan Sozuer, MD<sup>1,2</sup>

<sup>1</sup>Department of General Surgery, Erciyes University Medical Faculty, Melikgazi, Kayseri, Turkey

<sup>2</sup>Department of Surgical Oncology, Erciyes University Medical Faculty, Melikgazi, Kayseri, Turkey

<sup>3</sup>Department of Pathology, Erciyes University Medical Faculty, Melikgazi, Kayseri, Turkey

# Abstract

**Background:** Our aim was to investigate the pathologies in the hernia sac in adults, and the frequency of malignancy as well as to confirm the necessity of maintaining the current applications in histological examination of the hernia sac.

**Methods:** Patients who were operated for hernia in our clinic from 2013 to 2019 were included in the study. Patient data were evaluated retrospectively. We divided the patients into four groups, according to the type of hernia. We evaluated the demographic characteristics of the patients, the pathologies within the hernia sac, histopathological examination outcomes of the hernia sac and clinical features of malignancy in patients with malignancy.

**Results:** A total number of 556 adult patients underwent inguinal, femoral, umbilical or incisional hernia repair in our hospital. Nine patients (0.61%) had malignancy in the hernia sac. Three out of nine patients (33%) had no preoperative diagnosis of malignancy. Six patients (67%) had a known history of malignancy. Two tumors were located in the inguinal (22.0%), six tumors in the incisional (67%), and one in the umbilical (11%) hernia sacs. Among these, 56% were of gastrointestinal, 22% of gynecological, 11% of breast and 11% of epididymis origin. Most of the other pathologies found in the hernia sac were herniated bowel segments, lipomas and omentum.

**Conclusion:** Since the hernia sac might be the first clue for an underlying cancer, if abnormal pathological findings are detected during surgery, histopathological examination should be performed to exclude malignancy. The purpose of histological examination is to detect a hidden malignancy

Keywords: Carcinoma, Hernia, Metastasis, Pathology surgical

**Cite this article as:** Topal U, Gok M, Akyuz M, Oz AB, Arıkan TB, Solak İ, et al. Is histopathological evaluation of hernia sacs necessary? Arch Iran Med. 2020;23(6):403–408. doi: 10.34172/aim.2020.34.

Received: August 20, 2019, Accepted: December 15, 2019, ePublished: June 1, 2020

# Introduction

Hernia repair is one of the most common surgical procedures in all age groups. The histopathological examination of a hernia sac specimen may rarely reveal an unexpected diagnosis.

Hernia sac is a common sample that can provide a wide range of pathological findings in surgical pathology. However, the need for routine microscopic examination is still being debated. There are studies which show that a routine presentation of pediatric inguinal hernia sacs is not necessary due to the low efficiency of unexpected findings.<sup>1</sup> For adults, some institutions do not routinely perform microscopic examination of inguinal hernia sacs, but often examine abdominal wall hernias.<sup>2,3</sup>

The American College of Pathologists recommends the presentation of all adult hernia sac specimens to the pathology, but it leaves the decision of performing a microscopic examination of inguinal hernia sacs in adults and the umbilical hernias in children to the pathologist/ institution.<sup>4</sup> In the previous literature, in their series of 1426 cases, Wang et al found the incidence of malignancy at 0.4% in inguinal hernias and 1.2% in incisional hernias.<sup>3</sup>

Our institute is a center where both macroscopic and microscopic examinations of all hernia sacs are routinely performed. In this study, we aimed to investigate the pathological findings and the incidence of malignancy in the hernia sac in adults and to confirm the necessity of maintaining current practices in the histological examination of the hernia sac.

# Material and Methods

A total of 556 patients were included in the study who were operated on with diagnoses of umbilical, incisional, femoral, and inguinal hernia in the Erciyes University Faculty of Medicine Hospital in Kayseri, Turkey between January 2013 and January 2019.

Hernia was diagnosed by physical examination and imaging methods. Totally, 32 patients with incomplete medical records were excluded from the study. Patient

\*Corresponding Author: Ugur Topal, MD; Department of General Surgery, Erciyes University Faculty of Medicine, 38030 Melilgazi/Kayseri, Turkey. Tel: +90 530 1139112; Fax: +90 352 437 52 73; Email: sutopal2005@hotmail.com

data were evaluated retrospectively based on their medical records

We divided the patients into four groups based on the hernia type: Group 1 - inguinal hernia, group 2 - incisional hernia, group 3 - umbilical hernia, and group 4 - femoral hernia. The patients' age, sex, emergency or elective operation, and histopathological examination results were evaluated in groups.

Treatment management of patients who were found to have a pathology on histopathological examination were examined.

# Statistical Analysis

We used the IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) package program. Chisquare test was used to determine the relationship between patient groups and gender and operation status, while ANOVA analysis was used to determine the relationship between patient groups and age. Following the ANOVA analysis, Bonferroni method, one of the post hoc analysis types, was used to determine the source of differentiation between the groups. Statistical significance level was taken at 0.05 in all tests.

# Results

A total of 556 patients participated in our study. Every hernia specimen obtained in our institution was sent for pathological examination. There were 258 patients

Table 1. Hernia	Categories:	Age and	Sex	Distribution
-----------------	-------------	---------	-----	--------------

(46.4%) in group 1, 197 (35.3%) in group 2, 87 (15.6%) in group 3, and 14 (2.7%) in group 4 (Table 1).

The mean age was 54.4 years in group 1, 60.1 in group 2, 56.4 in group 3 and 71.6 in group 4, and the difference between them was statistically significant (P<0.001). The highest mean age was in group 4. The results of the Bonferroni correction on the differences between the groups are shown in Table 2.

In terms of gender distribution, male dominance was seen in group 1 (91.1%) and female dominance was seen in group 2 (75.7%) and group 3 (70.2%), while group 4 was balanced in this regard (P<0.001).

In all groups, operations under elective conditions were significantly higher than emergency operations (P < 0.001) (Table 1).

Looking at the pathological examination of the hernia sacs in group 1, the most common outcome was "no pathology or only inflammation" in 176 (68.2%) patients, and lipoma in 61 (23.6%) patients, while papillary cystadenoma, mucinous neoplasm with uncertain malignant potential, and mesothelial hyperplasia were each found in 1 patient (Table 3). In group 2, "no pathology or only inflammation" was seen in 165 (83.8%) cases and carcinoma metastasis was seen in 3%. The etiological cause was gastric in two patients, and ovarian in two patients, while gallbladder and breast cancer origins were each found in 1 patient (Table 3). In group 3, 76 (87.3%) cases had "no pathology or only inflammation"

Parameters	Group 1 (n = 258)	Group 2 (n = 197)	Group 3 (n = 87)	Group 4 (n = 14)	P Value
Age (mean) + SD (min-max)	54.4 + 17.7 (11-93)	60.1 + 12.4 (18-89)	56.4+13.7 (18-89)	71.6 + 13.5 (47–87)	0.001
Sex					0.001
Female	23	149	61	8	
Male	235	48	26	6	
Operation					0.001
Emergency	47	39	16	6	
Elective	211	158	71	8	

ANOVA and chi-square test were used.

# Table 2. Results of Bonferroni Correction for Age

		Maan Differences	D Value	95% Cl		
		Mean Differences	r value	Lower	Upper	
	Inguinal hernia	17.228*	0.000	4.084	28.373	
Femoral hernia	Incisional hernia	11.4906*	0.042	0.258	22.724	
	Umbilical hernia	15.206*	0.004	3.511	26.901	
	Femoral hernia	-17.2281*	0.000	-28.373	-6.084	
Inguinal hernia	Incisional hernia	-5.7376*	0.001	-9.580	-1.895	
	Umbilical hernia	-2.0221	1.000	-7.057	3.013	
	Femoral hernia	-11.4906	0.042	-22.724	-0.258	
Incisional hernia	Inguinal hernia	5.7376*	0.001	1.895	9.580	
	Umbilical hernia	3.7155	0.362	-1.512	8.943	
	Femoral hernia	-15.206*	0.004	-26.901	-3.511	
Umbilical hernia	Inguinal hernia	2.0221	1.000	-3.013	7.057	
	Incisional hernia	-3.7155	0.362	-8.943	1.512	

Post hoc pair-group analysis was performed using Bonferroni correction (\*P<0.05).

Diagnosis	Inguinal Hernias	Incisional Hernias	Umbilical Hernias	Femoral Hernias
Diagnosis	(n = 258)	(n = 197)	(n = 87)	(n = 14)
No pathology or only inflammation	176	165	76	8
Necrosis of small bowel segment	10	12	3	6
Omentum majus	5	14	6	0
Appendix vermiformis	2	0	1	0
Lipoma	61	0	0	0
Gastric adenocarcinoma*	0	2	0	0
Gall bladder adenocarcinoma*	0	1	0	0
Ovary carcinoma*	0	2	0	0
Breast carcinoma (lobular)*	0	1	0	0
Gastrointestinal stromal tumor*	0	0	1	0
Granulomatous lymphadenitis*	1	0	0	0
Papillary cystadenoma*	1	0	0	0
Mucinous neoplasm with uncertain malignant potential*	1	0	0	0
Mesothelial hyperplasia*	1	0	0	0

Table 3. Pathology in Hernias

\*Pathologies diagnosed after histological examination.

and one patient had gastrointestinal stromal tumor (Table 3). In group 4, 8 (57.2%) cases had "no pathology or only inflammation" and 6 (42.8%) cases had necrosis of small bowel segment (Table 3). The previous clinical history and clinical features of the patients who had malignancy in the hernia sac are given in Table 4.

Histopathological examination of lobular breast carcinoma is shown in Figure 1. Histopathological examination of gastric carcinoma is shown in Figure 2. Histopathological examination of ovary carcinoma is shown in Figure 3.

## Discussion

A tumor within the hernia sac was first reported by Arnaud G in 1749.<sup>5</sup> In the literature, many benign and malignant pathologies have been reported in different rates in hernia sacs.<sup>1,3</sup> Gastrointestinal malignancies, especially colon adenocarcinomas, are the most common carcinomas detected in the hernia sac. However, tumors within the hernia sac are associated with a wide range of tumor types. Other carcinomas reported within the hernia sac include ovarian cancer, melanoma, rectal cancer, pancreatic cancer, Non-Hodgkin lymphoma, gallbladder cancer, liposarcoma, prostate cancer, breast cancer, and neuroendocrine carcinoma.<sup>3,6-9</sup> In their series of 8435 patients, Val-Bernal et al found that the malignancy rate in pathological examination of hernia sacs was 0.12%.<sup>10</sup>

Routine examination of hernia sacs was not found to be cost effective in the literature. Therefore, there is controversy about the need for all hernia sac specimens to be presented for histological examination. There are opinions supporting an evaluation of abnormal tissue samples that suggest an underlying disease process discovered during surgery.<sup>1,11</sup>

The American College of Pathologists recommends the presentation of all adult hernia sac specimens to the pathology, but it leaves the decision of performing a microscopic examination of inguinal hernia sacs in adults and the umbilical hernias in children to the pathologist/ institution.<sup>6</sup>

Some authors advocate routine histological examination of hernia sacs, as a secret malignant lesion may be

Table 4.	Clinical a	and F	athological	Features	of	Malignancies	Detected i	n l	Hernia	Sac
----------	------------	-------	-------------	----------	----	--------------	------------	-----	--------	-----

Age	Sex	Diagnosis	Lesion Seen Grossly	Clinical comment			
Inguinal Hernias							
60	F	Mucinous neoplasm with uncertain malignant potential	Yes	Unknown before the operation, no history of malignancy, appendix origin			
63	М	Papillary cystadenoma	Yes	Unknown before the operation, epididymis origin			
			Incisional Hernias				
58	М	Gastric adenocarcinoma	No	Known history of gastric adenocarcinoma			
78	F	Gastric adenocarcinoma	Yes	Known history of gastric adenocarcinoma			
57	F	Gallbladder adenocarcinoma	Yes	Known history of gallbladder adenocarcinoma			
59	F	Ovarian carcinoma (serous)	Yes	Known history of ovarian carcinoma			
59	F	Ovarian carcinoma (serous)	Yes	Known history of ovarian carcinoma			
65	F	Lobular Carcinoma of breast	No	Known history of lobular carcinoma of breast			
Umbilical Hernias							
69	F	Gastrointestinal stromal tumor	Yes	Unknown before the operation, stomach origin			

Femoral hernias no malignancy. M, Male; F, Female.



**Figure 1.** (A) Malignant Tumor Infiltration in the Hernia Sac (Lobular Breast Carcinoma) (H&E, X100). (B) Nuclear Estrogen Positivity in Immunohistochemical Examination (H&E, X100).



Figure 2. Malignant Gland Structures Infiltrating the Hernia Sac (Gastric Carcinoma) (H&E, X40).

found during histopathological examination, even if the macroscopic examination of the hernia sac appears to be normal. Additionally, microscopic examination of hernia sacs may provide a unique opportunity for peritoneal biopsy.

Hernia repair is one of the most common surgical interventions worldwide. Looking at the demographic characteristics in our series, femoral hernias were seen in advanced age compared to other hernias (P = 0.0001). Male gender was dominant in inguinal hernias and female sex was dominant in the other hernia types (P = 0.001). While 80% of cases had elective surgery for inguinal, umbilical and incisional hernias, this rate was decreased in femoral hernias, and 42% of femoral hernias underwent emergency surgery (P = 0.001).

We found inflammation as the most common cause in pathological examinations of the hernia sac in all hernia varieties. This inflammation is a benign finding due to chronic irritation of the hernia sac. This may reflect a longstanding situation and has no effect on the management of the patient.

The presence of appendix vermiformis in the inguinal hernia sac is rare, and reported at 0.6–1% in the literature.<sup>12-15</sup> In our series, two (0.77%) patients had appendix vermiformis which was not inflamed; therefore, we did not perform an appendectomy. The lipoma of the cord detected in the inguinal hernia sac indicates an anatomical variant of this region rather than a true neoplasm.<sup>16</sup> In our series, the rate of cord lipoma was 23%. Wang et al found the incidence of malignancy in inguinal hernia sacs at 0.4% in their series.<sup>3</sup> It was 0.76% in our study. We found two malignancies. One of them was mucinous neoplasm with uncertain malignant



**Figure 3.** (A) Malignant Gland Structures and Papillary Structures Infiltrating the Hernia Sac (Ovarian Carcinoma) (H&E, X100). (B) Nuclear WT1 Positivity in Cells by Immunohistochemical Examination (H&E, X100).

potential. Intraoperatively, there was a macroscopic mass formation. It was found to originate from the appendix. Therefore, appendectomy was performed in the second operation. The other patient had papillary cystadenoma. Intraoperatively, the cystic mass was 2 cm in diameter and was excised. Pathological examination reported epididymis origin.

Wang et al found the malignancy rate in hernia sacs of abdominal wall hernias at 1.2%. The most common source in their series was ovarian origin, and there were also tumors of the prostate and pancreas.<sup>3</sup> In our study, we found it at 3%, which originated from the stomach, ovary and gallbladder.

Gallbladder carcinomas are a rare malignancy with poor prognosis. More than 80% of cases cannot be resected and only 5% of patients survive for 5 years. Previously, there have been cases diagnosed with gallbladder cancer metastasis in the incisional hernia sac.<sup>17,18</sup> In our series, histopathological examination of the incisional hernia sac revealed gallbladder cancer metastasis in one patient. This patient had a history of gallbladder cancer and did not have a diagnosis of peritoneal carcinomatosis; this diagnosis was made by hernia sac examination.

In a series of 3117 patients by Robert et al, one patient was found to have lobular breast carcinoma metastasis in the histopathological examination of the hernia sac. We also found a patient with lobular carcinoma metastasis in our study. A 65-year-old woman, who was previously known to have breast cancer, had no gross lesion in the macroscopic examination of the hernia sac. A diagnosis of peritoneal carcinomatosis was not known in this patient; the diagnosis was made by histopathological examination of the hernia sac.<sup>19</sup>

In their series of 8435 patients Val-Bernal et al found two patients with gastric tumor metastasis to the hernia sac. In the same study, when malignancy cases in the literature were examined, gastric metastasis was seen to constitute 5.3% of all malignant metastases.<sup>10</sup> In our series, metastasis originating from gastric cancer was detected in two patients within the incisional hernia sac. One of these patients had macroscopic findings and the other did not. The two patients were previously known to have gastric cancer.

In a series of 3117 patients, Robert et al found

gynecologic malignancies as the origin in 45% of herniated sacs detected as malignancy.<sup>19</sup> In our series, malignancy of this origin in incisional herniation was 33%, found in two patients. There were two patients with a history of ovarian cancer, and their macroscopies revealed tumoral implants.

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the digestive tract. The most common origin is the stomach, with 60%-70%. They are rarely present in the abdominal peritoneum, hernia sac or mesentery, and usually present as metastases of the primary disease originating from the gastrointestinal tract. They have been previously reported in the inguinal hernia sac in the literature.<sup>20,21</sup> In our study, during the umbilical hernia repair, a patient had a macroscopically visible mass formation attached to the sac within the hernia sac. When the abdomen was explored, it was determined that this mass was of gastric origin. Wedge resection was performed. It was not previously known that the patient had a stromal tumor before the operation. In our series, other umbilical hernia pathologies were omentum and bowel segment with necrosis.

Femoral hernias constitute up to 5% of all inguinal hernias. They are 3–4 times more common in women. They usually occur in middle and advanced ages. The rate of strangulation in the literature is reported to be between 30%-40%.<sup>22-25</sup> In our study, femoral hernias were statistically significantly seen at a more advanced age and were more frequent in females compared to other hernias (*P* = 0.001). We did not detect any malignancy in any of the hernia sacs. There was a strangulated bowel segment in 42% of the hernia sac specimens.

Routine histological examination of all hernia sacs may have some justification when it comes to legal, medical and quality control reasons. However, few positive results were obtained from the patients with the routine test of all hernia sacs which appear normal in the operation.

Any patient with a history of intra-abdominal malignancy presenting with a new hernia should be examined for tumor recurrence. If abnormal pathological findings are detected during surgery, histopathological examination should be performed to exclude malignancy. The purpose of the histological examination is to detect a hidden malignancy.

In conclusion, the results of our study provide evidencebased support to the current guidelines of the College of American Pathologists, which recommends the microscopic examination of every abdominal wall hernia, but leaves the microscopy of inguinal hernias at the discretion of the institution/pathologist.

#### **Authors' Contribution**

UT and IS: Conceived, designed and editing of manuscript. UT and MA: Manuscript writing. ABO, TBA, MG and KD: Taking responsibility in logical interpretation and presentation of the results. MA and ES: Did review and final approval of manuscript.

# **Conflict of Interest Disclosures**

The authors have no conflicts of interest.

### **Ethical Statement**

Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 22.05.2019, number: 2019/369).

#### References

- Kim B, Leonard MP, Bass J, Ruzhynsky V, de Nanassy J, Guerra L. Analysis of the clinical significance and costassociated with the routine pathological analysis of pediatric inguinal hernia sacs. J Urol. 2011;186(4):1620-4. doi: 10.1016/j. juro.2011.03.071.
- Matthyssens LE, Ziol M, Barrat C, Champault G. Routine surgical pathology in generalsurgery. Br J Surg. 2006;93(3):362-8. doi: 10.1002/bjs.5268.
- Wang T, Vajpeyi R. Hernia sacs: is histological examination necessary? J Clin Pathol. 2013;66(12):1084-6. doi: 10.1136/ jclinpath-2013-201734.
- College of American Pathologists. Surgical specimens to be submitted to pathology for examination. Available from: https:// www.pathology.med.umich.edu/intra/Inspection\_Resources/ General%20Information/Surgical%20Specimens%20to%20 be%20Submitted%20to%20Pathology.pdf.
- 5. Arnaud G. Traite des herniaes ou descentes. Paris, Le Mercier. 1749;2:3.
- Nicholson CP, Donohue JH, Thompson GB, Lewis JE. A study of metastatic cancer found during inguinal hernia repair. Cancer. 1992; 69: 3008-11. doi: 10.1002/1097-0142(19920615)69:12<3008::aidcncr2820691224>3.0.co;2-8.
- Kassan MA, Munoz E, Laughlin A, Margolis IB, Wise, L. Value of routine pathology in herniorrhaphy performed upon adults. Surg Gynecol Obstet. 1986;163(6):518–22.
- Lowenfels A, Rohman M, Ahmed N, Lefkowitz M. Herniasac cancer. Lancet. 1969;1(7596):651. doi: 10.1016/s0140-6736(69)92013-3.
- 9. Goonewardena JN, Gallant V. Metastatic implants in hernial sacs. Ceylon Med J. 1977;22(2):96-8.
- Val-Bernal JF, Mayorga M, Fernández FA, Val D, Sánchez R. Malignant epithelial tumors observed in hernia sacs. Hernia. 2014;18(6):831-35.doi:10.1007/s10029-014-1283-z.
- Al Nemer A M, Al-Buainain H. The necessity of routine histologic examination of hernia sac, revisited. Hernia. 2015;19(6):915-8. doi: 10.1007/s10029-014-1338-1.
- D'Alia C, Lo Schiavo MG, Tonante A, Taranto F, Gagliano E, Bonanno L, et al. Amyand's hernia: case report and review of the literature. Hernia. 2003;7(2):89-91. doi: 10.1007/s10029-002-0098-5.
- 13. Thomas WEG, Vowles KDJ, Williamson RCN. Appendicitis in external herniae. Ann R Coll Surg Engl. 1982;64(2):121-2.
- 14. Lombardo V, Pavone G. Intraoperative finding of Amyand's hernia in a recurrent inguinal hernia: report of a case. Ann Ital Chir. 2013;84(5):583-4.
- Maternini M, Gabrielli F, Pecora N, Riggio V, Chiarelli M, Guttadauro A. Amyand Hernia in an elderly patient. Ann Ital Chir. 2018;7(1):1-3.
- 16. Carilli S, Alper A, Emre A. Inguinal cord lipoms. Hernia. 2004;8(3):252-54. doi: 10.1007/s10029-004-0231-8.
- Spencer AL, Jones FK, Birdsong GG, Bumpers HL. Gallbladder cancer presenting as an incisional hernia. Surg Rounds. 2007;30(1):33.
- 18. Jones RS. Carcinoma of the gallbladder. Surg Clin North Am. 1990;70(6):1419-28. doi: 10.1016/s0039-6109(16)45292-8.
- 19. Roberts JA, Ho D, Ayala AG, Ro JY. A study of metastatic

carcinoma found in hernia sacs between 2006 and 2012 at one institution. Ann Diagn Pathol. 2014;18(2):71-3. doi: 10.1016/j.anndiagpath.2013.10.008.

- Liu PH, Kung WC, Wu YC, Chien ST, Chang WY, Hsu CW. Metastatic malignant gastrointestinal stromal tumor mimicking a right incarcerated inguinal hernia. Formos J Surg. 2014;47(5):189-92. doi: 10.1016/j.fjs.2014.04.003.
- 21. Ferhatoglu MF, Kartal A, Kivilcim T. Gastrointestinal stromal tumor mimicking such as incarcerated inguinal hernia. MSD. 2018;5(3):166-8. doi: 10.17546/msd.407478.
- 22. Hachisuka T. Femoral hernia repair. Surg Clin N Am. 2003;83(5):1189-205. doi: 10.1016/S0039-6109(03)00120-8.
- 23. Oishi S, Page C, Schwesinger W. Complicated presentations of groinhernias. Am J Surg. 1991;162(6):568-70. doi: 10.1016/0002-9610(91)90110-y.
- Álvarez-Pérez JA, Baldonedo-Cernuda RF, García-Bear I, Suárez-Solís JA, Álvarez-Martínez P, Jorge-Barreiro JI. Presentation and clinical evolution of incarcerated groin hernias in adults. Cir Esp. 2005;77(1):40-5. doi: 10.1016/ S0009-739X(05)70802-2.
- 25. Engin O, Cicek E, Oner SR, Yildirim M. Incarcerated femoral hernia containing the right uterine tube. A pre-operative diagnosis is possible. Ann Ital Chir. 2011;82(5):409-12.

© 2020 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons. org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.